New Drug Approved to Help Agriculture's Helpful Honey Bees

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Honey bees are big money makers for U.S. agriculture. These social and hardworking insects produce six hive products – honey, pollen, royal jelly, beeswax, propolis, and venom – all collected and used by people for various nutritional and therapeutic purposes.

Honey, of course, is the most well-known and economically important hive product. According to the U.S. Department of Agriculture's (USDA) National Agriculture Statistics Service, honey bees made more than 148 million pounds of honey last year. With the cost of honey at a record high at about $1.73 per pound, that's a value of over $256 million.

After honey, beeswax is the second most important hive product from an economic standpoint. The beeswax trade dates to ancient Greece and Rome, and in Medieval Europe, the substance was a unit of trade for taxes and other purposes. The market remains strong today. Beeswax is popular for making candles and as an ingredient in artists' materials and in leather and wood polishes. The pharmaceutical industry uses the substance as a binding agent, time-release mechanism, and drug carrier. Beeswax is also one of the most commonly used waxes in cosmetics. The U.S. is a major producer of raw beeswax, as well as a worldwide supplier of refined beeswax.

Honey bees are like flying dollar bills buzzing over U.S. crops.

But the greatest importance of honey bees to agriculture isn't a product of the hive at all. It's their work as crop pollinators. This agricultural benefit of honey bees is estimated to be between 10 and 20 times the total value of honey and beeswax. In fact, bee pollination accounts for about $15 billion in added crop value. Honey bees are like flying dollar bills buzzing over U.S. crops.

Luckily for the honey bees and the many crops that depend on them for pollination, FDA recently approved a new drug to control American foulbrood, a widespread bacterial disease that kills bee larvae.

The Biology of Pollination

Pollination is vital to the approximately 250,000 species of flowering plants that depend on the transfer of pollen from flower anther to stigma to reproduce. The anther is the top-most part of the stamen, the flower's male reproductive portion. Normally made up of four pollen sacs, the anther produces and releases pollen. The stigma, the flower's female reproductive part, is covered in a sticky substance that catches and traps the pollen grains.

Depending on the specific plant species, the transfer of pollen from anther to stigma is achieved by wind, gravity, water, birds, bats, or insects. Some plants, such as pine trees and corn, produce light pollen that's easily blown by wind. Other plants make heavy, sticky pollen that's not easily blown from flower to flower. These plants rely on other agents, insects for example, to transfer the pollen.

Upon entering a flower, an insect such as a honey bee, brushes against the pollen on the outside of the anther and carries it to the stigma. Sometimes, the pollen grains only need to reach the stigma of the same flower or another flower on the same plant. But often, the pollen must travel to the stigma of a flower on a different plant (but same plant species).

A Bee's Dinner Plate

Honey bees are vegetarians. Nectar and pollen collected from flowering plants are the entrees on their dinner plates. Bees harvest the nectar and convert the sugary liquid to honey, the insects' primary source of carbohydrates. Honey provides the bees with the energy for flight, colony maintenance, and general daily activities.

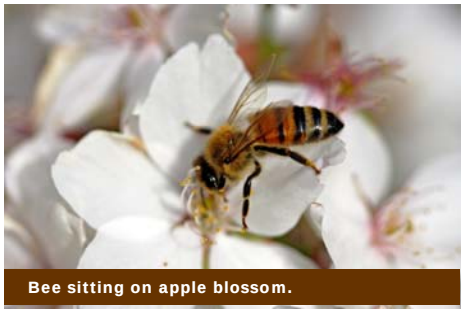
Pollen, often called "bee bread," is the bees' main source of protein. Pollen also provides the bees with fatty acids, minerals, and vitamins. The protein in pollen is necessary for hive growth and young bee development.

Pollen collected by bees

Depending on the season, weather, and availability of nectar- and pollen-bearing blossoms, the size of a honey bee colony varies from 10,000 to 100,000 bees. A typical size colony, made up of about 20,000 bees, collects about 125 pounds of pollen per year[1]. Bees carry the pollen in specialized structures on their hind legs called "pollen baskets," or *corbiculae* (meaning "little baskets" in Latin). A

[1]The number of bees in a typical size honey bee colony and the amount of pollen a colony collects per year vary between references. The source for this sentence is The Benefits of Pollen to Honey Bees by Ellis A, Ellis J, O'Malley M, et al. Entomology and Nematology Department, Florida Cooperative Extension, Institute of Food and Agricultural Sciences, University of Florida. *Publication #ENY152*. Original publication date September 2010.

honey bee can bring back to the colony a pollen load that weighs about 35 percent of its body weight.


Bee sitting on apple blossom.

In a single day, one worker bee makes 12 or more trips from the hive, visiting several thousand flowers. On these foraging trips, the bee can travel as far as two to five miles from the hive. Although honey bees collect pollen from a variety of flowers, a bee limits itself to one plant species per trip, gathering one kind of pollen.

Bees Fill American Dinner Plates

Honey bees are not native to the New World. Most crops grown in the U.S. aren't New World natives either. Both the crops and the bees evolved together in other areas of the globe, and were brought here by European settlers. Information suggests that the first honey bee colonies arrived in the Colony of Virginia from England early in 1622.

Today, the commercial production of more than 90 crops relies on bee pollination. Of the approximately 3,600 bee species that live in the U.S., the European honey bee[2] (scientific name *Apis mellifera*) is the most common pollinator, making it the most important bee to domestic agriculture. About one-third of the food eaten by Americans comes from crops pollinated by honey bees, including apples, melons, cranberries, pumpkins, squash, broccoli, and almonds, to name just a few. Without the industrious honey bee, American dinner plates would look quite bare.

Many Workers, Several Drones, and One Queen Bee

A honey bee colony is a highly organized society made up of three kinds of adult bees – workers, drones, and a single queen – each with specific roles. Worker bees are sexually undeveloped females and under normal hive conditions don't lay eggs. As suggested by their name, worker bees are the hive's laborers, performing all the tasks needed to maintain and protect the colony and rear the young bees. Despite being the smallest physically, they are by far the largest in number, making up nearly all the bees in a colony. A worker bee's life span ranges from six weeks in the busy summer to four to nine months during the winter.

Drones are male bees that are on standby for mating with a virgin queen, should the need arise. For the drones, death instantly follows mating. They number from a few to several thousand and are usually present only during late spring and summer.

[2]The European honey bee is also called the common or western honey bee.

As the lone sexually developed female in the colony, the queen's main function is to reproduce. She mates only once with several drones and remains fertile for life. The queen can live for several years, with an average productive life span of two to three years. When she dies or her productivity declines, worker bees raise a new queen.

Honey Bee Hives and Bee Brood

Derived from the Latin word *apis* meaning "bee," apiculture is the raising and caring of honey bee colonies by people. Beekeepers, or apiarists, house their domesticated honey bee colonies in man-made hives kept in an apiary, or "bee yard."

The basic structural component of the hive is a wax comb suspended within a plastic or wooden frame. Worker bees construct the comb using beeswax, a substance produced by four pairs of glands located on the underside of their abdomens. Secreted as a liquid, the substance hardens

A beekeeper's apiary, or bee yard."

Beekeeper inspecting a wax comb suspended within a wooden frame.

Normal bee brood and adult honey bees.

into flat wax scales once exposed to air. Using spines located on their middle legs, the bees remove the wax scales from their abdomens. The bees transfer the scales to their mouthparts, and while chewing the wax, they add salivary secretions to soften it. The bees then use the now pliable wax to build the hexagon-shaped cells of the comb.

Within the six-sided cells of the wax comb, the bees store honey and pollen and rear the bee brood, a collective term encompassing the three developmental stages of bees – egg, larval, and pupal. In the first stage, the queen deposits one egg in each cell. At peak production in spring and early summer, she may lay up to 1,500 eggs[3] per day. Fertilized eggs develop into female worker bees. Unfertilized eggs become male drones.

The egg hatches in three days to become a larva, a legless white grub. Sometimes called the feeding stage, the larval stage is one of rapid growth. While still inside its beeswax cell, the larva is fed by "nurse" worker bees. When the larva is a few days old, worker bees cap the cell with a beeswax cover. A healthy larva is plump and pearly white with a glistening appearance.

[3]The number of eggs a queen can lay in one day varies between references. The source for this sentence is the Mid-Atlantic Apiculture Research and Extensive Consortium (MAAREC) Web page, The Colony and Its Organization.

During the pupal, or transformation, stage, the grub-like larva changes into an adult bee. This metamorphosis occurs within the capped cell. A healthy pupa remains white and glistening during the early period of development, even though it's beginning to take on adult features. Depending on the kind of bee (worker, drone, or queen), it emerges from the cell 7½ to 14½ days after capping.

Beekeepers can assess the health of the bee brood by looking at brood patterns. The pattern of healthy capped worker brood is solid and compact with few empty cells. The cell cappings are medium brown and convex, with no punctures. Drone brood is normally in patches around the comb's margins.

Unfortunately, healthy brood patterns are becoming less common. Faced with several threats, honey bee populations in the U.S. are declining. These threats include parasites like the *Varroa mite*, pesticide exposure, Colony Collapse Disorder, and diseases such as American foulbrood.

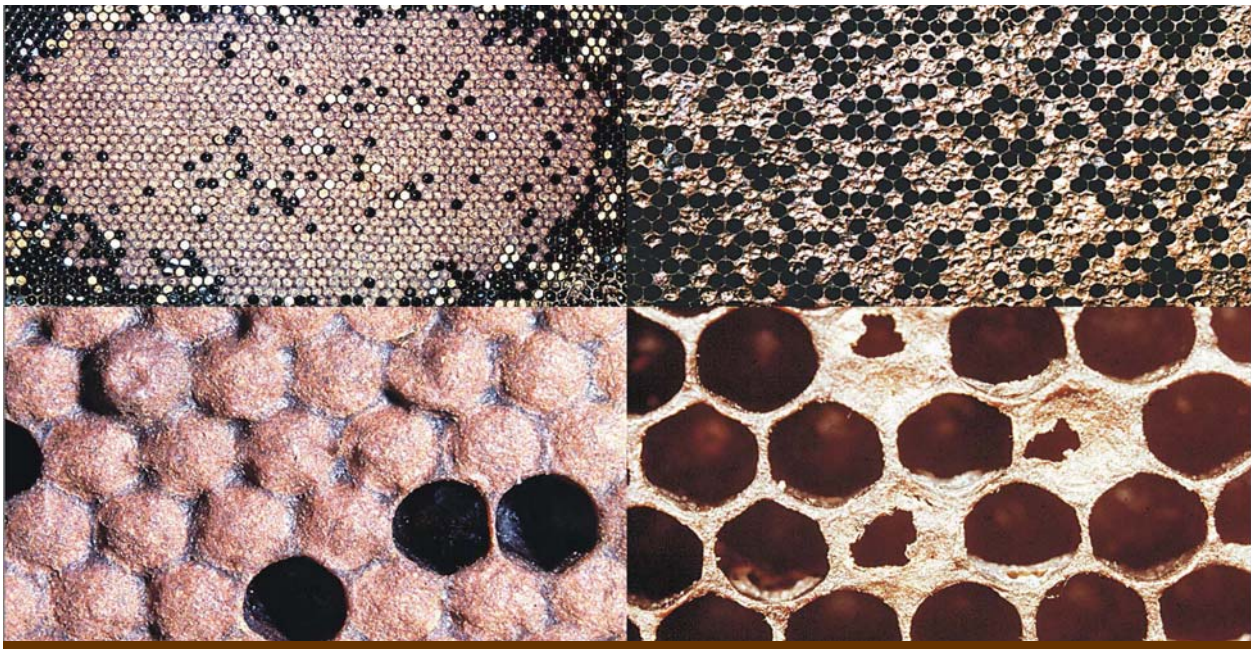
American Foulbrood – A Foul Disease

When beekeepers utter the three-letter acronym "AFB," they're not referring to the closest air force base. Rather, they're talking about American foulbrood, a serious infectious disease of honey bees. Caused by the spore-forming bacteria *Paenibacillus larvae* and found worldwide, AFB is one of the most widespread diseases affecting honey bee brood, and the most destructive. The disease does not pose any health risks to people, but it wreaks havoc among bees. Severe outbreaks can weaken or kill entire colonies.

American foulbrood affects the larval and pupal stages of brood development, leaving adult bees safe from infection. Young larvae may die quickly when they are curled at the base of their uncapped cells. Worker bees remove these dead larvae, leaving empty cells. Most often, death occurs after the cell has been capped. By this time, the older larvae or young pupae have stretched out lengthwise and are upright, filling most of their cell.

The capping of a cell that contains a diseased larva is moist and dark. As the larva shrinks, the capping is drawn into the mouth of the cell, causing the normally convex capping to become concave. When they find an infected larva in a sealed cell, worker bees puncture the sunken capping and remove it, along with the sick or dead larva.

If death occurs in the pupal stage, the dead pupa's threadlike proboscis, or

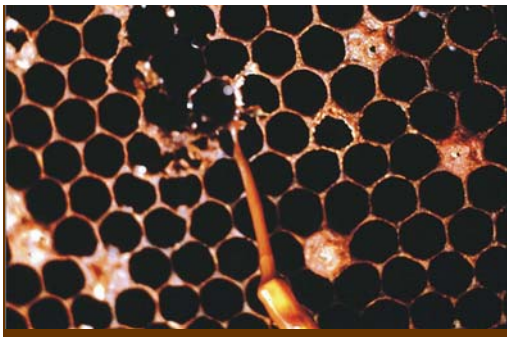


Normal frame on the left; AFB-infected frame on right. Normal brood pattern (top left) compared to patchy brood pattern seen in AFB (top right). Normal cell cappings that are closed and convex (bottom left) compared to diseased cell cappings that are sunken and punctured. Photo courtesy of USDA.

tongue, protrudes from the pupal head and extends across the cell. A protruding tongue can be seen even after the rest of the pupa's body has decayed. Though rarely seen, the formation of the pupal tongue is one of the most characteristic signs of American foulbrood.

At death, the normally pearly white and glistening bee brood changes to a dull white. The color gradually darkens to light creamy brown, then coffee brown, and finally dark brown or almost black. The consistency of the decaying brood is soft and glutinous. One symptom of American foulbrood seen only in decayed brood is "ropiness." When a probe is inserted into the body of a decayed larva and withdrawn gently and slowly, the glue-like larval remains will adhere to the tip of the probe and can be pulled out of the cell as a stringy, brown mass or rope. This technique used by beekeepers to assess ropiness is called the "match-stick" or "stretch" test. It's probably the best-known way to diagnosis AFB in the field. In some cases, however, the larval remains are rather watery, causing a negative test result.

One month or more after the larva becomes ropy, its remains dry out and shrivel to form hard, dark brown to black scales. These characteristic scales are brittle, stick tightly to the lower sides of the cell, and contain billions of spores that spread easily. The bacteria can produce over one billion spores in each infected larva. Only the spores are pathogenic (disease-causing), and unfortunately, they are very resistant to heat and chemicals. The spores of *P. larvae* can survive for many years in the dry



Glue-like remains of a decayed larva can be drawn out of a cell as a stringy, brown rope in the "match-stick" or "stretch" test for AFB. Photo courtesy of USDA.

scales, as well as in honey, beeswax, and hive equipment.

Nurse bees transmit American foulbrood by feeding spore-laden honey or bee bread to young larvae. Larvae can also become infected by *P. larvae* spores remaining at the base of their cells. "House" worker bees spread the spores throughout the hive when they clean out the cells of dead larvae.

The disease spreads quickly to other colonies in the apiary by:

- Robber bees. Weak, AFB-infected colonies make good targets for robber bees from nearby strong colonies. The robbers steal the contaminated honey or bee bread from the infected colony and bring the *P. larvae* spores back to their home colony.
- Beekeepers. While working with their hives, beekeepers may expose other colonies in the apiary to contaminated honey or equipment.
- Drifting worker bees or swarms. These bees are in the process of leaving their parent colony to start their own colony in a new location. If the parent colony is infected, the swarm will bring the spores with them to the new location.

A colony infected with American foulbrood has a patchy brood pattern. This irregular, mottled appearance is due to the mixture of healthy, diseased, and empty brood cells within the same wax comb. The healthy cells have slightly protruding and fully closed cappings. The diseased cells may be uncapped and contain larval remains, or still sealed but have sunken and punctured cappings. The empty cells are a result of worker bees chewing away the cappings of diseased cells and removing the dead larvae. The brood pattern is also patchy because the larval remains vary from the initial state of moist ropiness to the final state of dry scales adhered to the lower sides of open cells. A patchy brood pattern alerts the beekeeper that the colony is unhealthy, and while not diagnostic for American foulbrood, it raises the suspicion for this disease.

Controlling American Foulbrood

The traditional control measure for American foulbrood is to kill all bees in an infected colony and then burn the dead bees and hive materials belonging to the colony. Destroying the wax comb is critical because, apart from the bees, combs are the main carriers of *P. larvae* spores. Burning entire honey bee colonies and their hive materials is expensive, especially considering the high cost of beekeeping equipment.

Larger beekeeping operations often turn to drugs to help control American foulbrood, giving the bees antibiotics in their feed. While the antibiotics don't kill the spores, they do prevent the bacteria from multiplying.

For decades, the only FDA-approved drug to control American foulbrood was the antibiotic oxytetracycline[4]. But in October 2005, FDA approved a second antibiotic, tylosin tartrate, to control the disease. Due in large part to the work of NRSP-7[5], there are now three tylosin tartrate products approved for honey bees:

- TYLAN Soluble, sponsored by Elanco Animal Health (NADA[6] 013-076);
- PHARMASIN Soluble, also called TYLOVET Soluble, sponsored by Huvepharma AD (ANADA[7] 200-473); and
- TYLOMED-WS Soluble Powder, sponsored by Cross Vetpharm Group Ltd. (ANADA 200-455).

Both PHARMASIN Soluble and TYLOMED-WS Soluble Powder are generic copies of TYLAN Soluble.

The most recent antibiotic to be added to the beekeeper's arsenal against American foulbrood is lincomycin hydrochloride. In March 2012, FDA approved LINCOMIX Soluble Powder, sponsored by Pharmacia and Upjohn Co., a Division of Pfizer, Inc. (NADA 111-636). Studies to support the drug's approval were done by the Bee Research Laboratory, part of USDA's Agricultural Research Service, in Beltsville, Md., in cooperation with NRSP-7. Based on the results of these studies, FDA concluded that LINCOMIX Soluble Powder is safe and effective to control American foulbrood in honey bees when used according to the label.

LINCOMIX Soluble Powder is mixed with powdered sugar and applied as a dust inside the bee colony once weekly for three weeks. The bees consume the sugar-lincomycin mixture to clean the hive. During feeding, the nurse bees pass the drug to the larvae.

Similar to other drugs approved for honey bees, LINCOMIX Soluble Powder is fed in early spring or late fall before the main honey flow begins to avoid contamination of production honey. The three weekly treatments should be completed at least four weeks before the start of the main honey flow.

[4]Four sponsors have oxytetracycline products approved for the control of American foulbrood in honey bees. The products are marketed under several NADA and ANADA numbers and under several trade names. The sponsors are Pfizer, Inc. (NADA 008-622), Phibro Animal Health (NADA 008-804 and NADA 095-143), Pennfield Oil Co. (NADA 138-938 and ANADA 200-026), and Teva Animal Health, Inc. (ANADA 200-247). See Animal Drugs @ FDA for more information.
[5]NRSP-7: National Research Support Project No. 7, also called the Minor Use Animal Drug Program (MUADP)
[6]NADA: New Animal Drug Application
[7]ANADA: Abbreviated New Animal Drug Application

A Perilous Future

Honey bees are indispensable to U.S. agriculture, yet their future and the future of the dependent agricultural economies are perilous. The apiculture industry continues to battle the accelerating rate of decline in the health and number of honey bee colonies. With the recent FDA approval of LINCOMIX Soluble Powder to control American foulbrood, the battle has hopefully become a little easier.

References

Bogdanov S. The Bee Products

National Agricultural Statistics Service, Agricultural Statistics Board, USDA. Annual Report on Honey. Released March 30, 2012

Bogdanov S. Beeswax: History, Uses and Trade, in Online Beeswax Book: Chapter 2. Bee Product Science, http://www.bee-hexagon.net/. January 15, 2012.

CBI[8] Ministry of Foreign Affairs of the Netherlands. Promising EU export markets for vegetable oils, fats and waxes for cosmetics. June 2011.

Sanford MT. Protecting Honey Bees From Pesticides. Entomology and Nematology Department, Florida Cooperative Extension, Institute of Food and Agricultural Sciences, University of Florida. *Publication #CIR534*. Original publication date April 1993. Revised May 2003. Reviewed by Jamie Ellis, September 2011.

Flores A. Improving Honey Bee Health. *Agricultural Research*. February 2008.

Dictionary of Botany

Mid-Atlantic Apiculture Research and Extension Consortium (MAAREC). Pollination. *MAAREC Publication 5.2*. February 2000.

Ellis A, Ellis J, O'Malley M, et al. The Benefits of Pollen to Honey Bees. Entomology and Nematology Department, Florida Cooperative Extension, Institute of Food and Agricultural Sciences, University of Florida. *Publication #ENY152 (IN868)*. Original publication date September 2010.

Back Yard Beekeepers Association. Facts About Honeybees.

MAAREC. Bees Are Beneficial. *MAAREC Publication 1.1*. February 2000.

[8]CBI: Centre for the Promotion of Imports from developing countries

MAAREC. The Value of Honey Bees in the Mid-Atlantic Region.

Hackett KJ. Bee Benefits to Agriculture, in Forum. *Agricultural Research*. March 2004.

Oertel E. History of Beekeeping in the United States. Beekeeping in the United States, Agriculture Handbook Number 335; pp. 2-9. Revised October 1980.

The Pollinating Insects – Biology, Management and Systematics Research Unit, Agricultural Research Service, USDA. Research Strategy.

The University of Arizona Africanized Honey Bee Education Project. Africanized Honey Bees on the Move Lesson Plans.

MAAREC. Beekeeping equipment.

Beeswax Co., L.L.C. How Bees Make Wax.

MAAREC. The Colony and Its Organization.

Flores A. Helping Beekeepers Beat American Foulbrood. *Agricultural Research*. July 2007.

Bee Research Laboratory, Agricultural Research Service, USDA. American Foulbrood Disease.

Feldlaufer MF. Honey Bees Get a New Antibiotic, in Science Update. *Agricultural Research*. July 2006.

World Organization for Animal Health (OIE). American Foulbrood of Honey Bees, in the web version of Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2011; Vol. 1, Part 2, Section 2.2., Chapter 2.2.2.; pp. 395-404.

Ritter W and Akratanakul P. Honey bee diseases and pests: a practical guide, 2006. FAO[9] Agricultural and Food Engineering Technical Report 4. ISSN 1814-1137.

MAAREC. Bee Diseases & Their Control. *MAAREC Publication 4.9*. Revised November 2005.

FDA. Freedom of Information Summary, Supplemental New Animal Drug Application, NADA 111-636, for LINCOMIX Soluble Powder. March 27, 2012.

[9]FAO: Food and Agriculture Organization of the United Nations